AMENDMENTS TO THE CLAIMS

Listing of the Claims

The following listing of claims replaces all previous listings or versions thereof:

1. (Currently amended) An ~~*in vivo* assay to screen~~method of screening for an anti-proliferative ~~drugs~~drug~~, the~~ comprising the steps of:

   (a) contacting cells of a primary cell culture or of an established cell line with a candidate substance,

   (b) subsequently or concomitantly with [[a]]contacting of the candidate substance, contacting the cells with a growth factor[[,]];

   (c) processing the cells for immunofluorescence staining to detect APPL1 and APPL2 using an anti-APPL1 and/or 2 antibody, or alternatively using GFP-tagged APPL proteins stably or transiently expressed by the cells via transfection[[,]];

   (d) assessing the degree of colocalisation of APPL1 and/or 2 and the growth factor, the solubilisation of APPL1 and/or 2 and their translocation to the nucleus[[,]];

   (e) repeating steps (b) to (d) with cells not previously treated with the candidate substance[[,]]; and

   (f) comparing the degree of colocalisation of APPL1 and/or 2 and the growth factor, the solubilisation of APPL1 and/or 2 and their translocation to the nucleus between the cells not previously treated with the candidate substance (untreated cells) and cells treated with the candidate substance (treated cells),

   wherein an altered degree of colocalisation of APPL1 and/or 2 and the growth factor, an altered solubilisation of APPL1 and/or 2 and/or their altered translocation to the nucleus in the treated vs. the untreated cells identifies the candidate substance as an anti-proliferative drug.

2. (Original) The assay of claim 1, wherein the growth factor is an epidermal growth factor (EGF) family, a fibroblast growth factor (FGF), a transforming growth factor-β (TGFs-β), a transforming growth factor-α (TGF-α), an insulin-like growth factor such as IGF-I and IGF-II, a tumour necrosis factor such as TNF-α and TNF-β, a vascular endothelial growth factor (VEGF), a nerve growth factor (NGF), a hepatocyte growth factor/scatter factor, pleiotrophin, oncostatin M (OSM), an angiogenic factor (angiogenin), an ephrin, an interleukin (IL) such as IL1-13, an interferon (INF) such as IFN-α,-β,-γ, a colony stimulating factor (CSF), erythropoietin (EPO), or a platelet-derived growth factor (PDGF).

3. (Currently amended) The assay of claim 1~~ or 2~~, wherein the growth factor and/or the antibody are/is labelled, preferably by fluorescence, and/or wherein step (d) of assessing (i) the degree of colocalisation, (ii) the solubilisation and (iii) the translocation is performed by fluorescence microscopy.

4. (Currently amended) An ~~Anti~~anti-proliferative drug[[,]] identified and/or isolated according to the ~~assay~~method of claim 1.

5. (Currently amended) ~~Use of the anti-proliferative drug of claim 4 in the manufacture of a pharmaceutical to treat~~A method of treating a cancer/tumour ~~diseases~~disease comprising contacting a subject with a cancer/tumour disease with an anti-proliferative drug identified and/or isolated according to the method of claim 1.

6. (Currently amended) ~~Use~~The method of claim 5, wherein the treatment occurs by an inhibition of proliferation and/or induction of apoptosis in cancer/tumour cells.

7. (Currently amended) An ~~*in vitro* assay to screen~~method of screening for an anti-proliferative ~~drugs~~drug~~, the assay~~ comprising the steps of:

   (a) isolating hermosomes from cells of a cell culture, in particular by density gradient centrifugation[[,]];

(b) restoring their functionality by contacting the hermesomes with cytosol, an ATP-regenerating system and either or both of GTP and GDP[[,]];

(c) modulating their function in cell proliferation and/or apoptosis by ~~substances that modulate 1) the recruitment of Rab5 on hermesome, 2) the activity of Rab5 and the release of APPL1 and/or APPL2 from hermesomes, and 3) the ability of the released APPL proteins to interact with the NuRD/MeCP1 complex or its associated factors such as p53,~~contacting with a candidate substance; and

(d) comparing the hermesomes isolated from cells previously treated with or without the growth factor (stimulated or non-stimulated cells), with or without [[a]]the candidate substance (treated or untreated cells) or exposed to a candidate substance after isolation.

8. (New) The method of claim 7, wherein the candidate substance modulates (i) the recruitment of Rab5 on hermesome, (ii) the activity of Rab5 and the release of APPL1 and/or APPL2 from hermesomes, and/or (iii) the ability of the released APPL proteins to interact with the NuRD/MeCP1 complex or its associated factors such as p53.